REMARKS

Following entry of this amendment, claims 1-11, 21-40, and 55-65 will be pending in this application. Claims 15-20, all of which depended from previously canceled claim 12, are canceled herein without prejudice. Claim 55 is currently amended. Support for the amendment can be found throughout the specification and claims as originally filed, e.g., at paragraph [0040]. No new matter has been added.

Applicants thank the Examiner for her telephonic interview with Todd Garcia on December 16, 2008. In this interview, the Examiner indicated that claims 55 and 56 were inadvertently included in the list of claims rejected for alleged lack of enablement.

35 U.S.C. § 112, first paragraph

Claims 1-3, 10, 11, and 55-65 were rejected as allegedly not enabled for the full scope of the claims. Applicants respectfully traverse.

The State of the Art and Predictability of the Art

The Office action relies on Omaye (Toxicol., 180:139-150, 200) as evidence that CO is toxic at 70 ppm. The Office contends that undue experimentation would be required to practice the claimed invention because:

> One of ordinary skill in the art would first need to determine what concentration of CO to use that would not provide toxicity since applicants envision concentrations of 10-3000 ppm and Omaye discloses that CO levels of 70 ppm is toxic ands the claims is open ended to any amount of CO.

Office action at page 5. The Office appears to rely on Table 2 (page 156) of Omaye to support its assertion that "70 ppm is toxic." However, Table 2 does not teach that 70 ppm of CO causes physiological effects under all conditions. Omaye states that "Table 2 lists examples of ambient CO concentrations, estimated carboxyhemoglobin levels that might result as steady-state exposure, and related human health effects" (p. 144, col. 1). That is, the effects listed in Table 2 are the result of long-term exposure to the indicated concentrations of CO, whereas the specification also contemplates more limited CO exposure. Omaye further teaches that "[e]ffects

of CO exposure vary with the concentration and duration" (p. 144, col. 1), and total CO exposure is reflected by carboxyhemoglobin levels (the percentage of hemoglobin in a subject's blood bound by CO rather than oxygen). According to Omaye, most subjects are "asymptomatic" below carboxyhemoglobin (COHb) levels of 10%" (p. 144, col. 1). Because Omaye teaches that the CO dosage received depends on both the concentration of CO inhaled and the duration of exposure, the art clearly understood that concentrations of 70 ppm or higher could be administered to individuals for limited periods of time without significant ill effects.

Further, applicants deny that even the steady-state effects of 70 ppm CO as disclosed by Omaye would deter one skilled in the art from administering CO because it would be too "toxic." Omaye states that the effects of chronic exposure to 70 ppm CO (corresponding to a COHb level of 10%) are "exhaustion in healthy people, more angina in patients, [and] headaches" (Table 2). Doctors administering CO to patients experiencing hemorrhagic shock would clearly be able to weigh any effects such as "exhaustion" or "headaches" (or potentially greater adverse effects) against the therapeutic value of CO in treating hemorrhagic shock, which can lead to multiple organ failure and death.

The prior art also demonstrates that CO exposure (measured as COHb level) of an individual administered a specified amount of CO for a period of time (and any related physiological effect) is highly predictable. Because CO is often viewed as a potential environmental toxin, CO exposure has been extensively studied for decades. As one example, Stewart, 1974, Scand. J. Respir. Dis. Suppl. 91:56-62 (previously submitted), states that "the amount of carbon monoxide absorbed during exposure is highly predictable," and provides a chart showing predicted and experimental values of COHb accumulation over time for various CO concentrations (see Figure 1). At an ambient concentration of 100 ppm CO (higher than the 70 ppm level the Office contends is "toxic"), individuals do not reach a 10% COHb level (below which Omaye indicates that subjects are "asymptomatic") until after more than five hours of continuous exposure. One could administer a large concentration of CO for a short period of time or a small concentration of CO for a short period of time and achieve the same level of CO exposure, as measured by COHb levels. For example, referring to Fig. 1 of Stewart, a patient

exposed to 50 ppm CO for 3 hours would have a COHb level of 5%. At a concentration of 500 ppm, less than 20 minutes would be required to achieve an equivalent 5% COHb level. One of skill in the art would appreciate that the "amount" of a pharmaceutical composition comprising CO that is administered by inhalation will depend not only on the concentration of CO inhaled but also the duration of inhalation, and that both variables (concentration and duration) can be adjusted to provide a proper dosage.

Working Examples and Guidance Presented

The specification provides working examples of CO's protective effect against hemorrhagic shock (see Example 1). Applicants exposed mice to 250 ppm CO for either 6.5 hours during hemorrhagic shock and resuscitation or for 4 hours during only the resuscitation period. This treatment prevented multiple organ injury in the rodent model of HS/R. Even though the concentration of CO used was higher than 70 ppm, the exposure was for a limited period time (as opposed to Omaye's Table 2, which lists effects of ambient, steady-state exposure to 70 ppm CO). One skilled in the art would be able to extrapolate from this example, using the additional guidance in the specification and knowledge in the art, to determine safe and effective dosages of CO to treat hemorrhagic shock.

Furthermore, the specification provides ample guidance that affirms the general knowledge in the art concerning the administration of CO. The specification teaches that CO can be administered at various concentrations "intermittently or continuously" (paragraph [0040]). The specification also contemplates that higher concentrations of CO can be administered for shorter periods of time to achieve a therapeutic effect:

> In a given day, CO can be administered continuously for the entire day, or intermittently, e.g., a single whiff of CO per day (where a high concentration is used), or for up to 23 hours per day, e.g., up to 20, 15, 12, 10, 6, 3, or 2 hours per day, or up to 1 hour per day.

Specification, paragraph [0040]. Further, the specification teaches methods of monitoring a patient's CO level by observing "(1) carboxyhemoglobin (COHb), which can be measured in venous blood, and (2) exhaled CO collected from a side port of the ventilator" (paragraph

[0058]). The specification also teaches that "CO exposure can be adjusted based upon the patient's health status and on the basis of the markers" (paragraph [0058]).

The Relative Skill of Those in the Art and the Quantity of Experimentation Necessary

The relative skill of those in the art at the time of filing would have been high. The relevant individual would have been a health care practitioner, e.g., a physician. Applicants submit that health care practitioners at the priority date had a high level of skill in administering drugs (even potentially toxic ones) to patients. To illustrate, one could point to any number of highly toxic compounds, such as cancer chemotherapeutics, inhaled oxygen (which can cause oxidative stress and lung damage), inhaled anesthetic gases, and inhaled nitric oxide, all of which can be dangerous in overly high doses. These substances are routinely successfully administered by physicians of ordinary skill.

The Office action states (at page 5) that "[t]he quantity of experimentation needed is undue experimentation." Applicants submit that this summary conclusion is inappropriate to begin discussion of an individual *Wands* factor. See MPEP 2164.06 ("The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether 'undue experimentation' is required to make and use the invention."). The Office action goes on to state that:

> One of ordinary skill in the art would first need to determine what concentration of CO to use that would not provide toxicity since applicants envision concentrations of 10-3000 ppm and Omaye discloses that CO levels of 70 ppm is toxic ands the claims is open ended to any amount of CO.

Office action at page 5. As demonstrated above, those skilled in the art at the time of filing appreciated that CO dosage depends not only on the concentration of CO, but also on the timing of the exposure. Those skilled in the art were also well aware of any physiological effects stemming from different levels of CO exposure. Therefore, very little experimentation would be required to determine safe amounts and timing of CO administration. Some experimentation may have been required to determine optimal effective dosages, but this determination is merely routine in the context of pharmaceutical testing.

Applicants submit that any experimentation required to perform the claimed methods would be merely routine, and not undue. The art at the time of filing clearly acknowledged that CO exposure depends not only on the concentration of CO, but also on the length of time exposed. Such factors predictably determine COHb levels in an exposed subject, and such COHb levels correlate to known and predictable physiological effects. One skilled in the art could predictably administer a high concentration of CO for a short period of time or a lower concentration of CO for a longer period of time to achieve the same effect. No undue experimentation would have been required to determine "safe" amounts of CO to administer, because the art clearly understood the physiological effects of various levels of CO exposure. Adverse effects could be acceptable relative to the beneficial effect of CO to alleviate systemic organ and tissue damage due to hemorrhagic shock. Additionally, the specification provides working examples of CO's effect in a rodent model, and also provides significant guidance in the form of suggested concentration and timing of CO administration. Based on the advanced state of the art regarding knowledge of CO effects, the known predictability of CO administration, the high level of skill of those in the art in administration of potentially toxic drugs (including inhaled gases), the minimal experimentation necessary to determine "safe" dosages, the working examples, and the significant guidance in the specification, applicants submit that the claims are enabled for their full breadth. Applicants therefore request reconsideration and withdrawal of the rejection for alleged lack of enablement.

35 U.S.C. § 102

Claims 1-3, 10, and 11 were rejected as allegedly inherently anticipated by Fujita et al., Nature Med., 7:598-604, 2001 ("Fujita"), as evidenced by Bar-Or et al., US 2005/0215468 ("Bar-Or"). Applicants respectfully traverse.

To anticipate a claim, a reference must teach, either expressly or inherently, every element of the claim. Fujita does not expressly teach every element of the claim, because Fujita provides no express teaching or suggestion of a patient suffering from hemorrhagic shock. Nowhere does Fujita mention or even suggest the disorder of hemorrhagic shock.

To establish inherency, the missing element must necessarily be present in the reference. See MPEP § 2112 IV. Treatment of hemorrhagic shock is not inherent in Fujita. The specification defines hemorrhagic shock as:

> shock brought on by a loss (e.g., an acute or chronic loss) of circulating blood volume and/or oxygen carrying capacity. Hemorrhagic shock followed by resuscitation (HS/R) causes a systemic inflammatory response and often leads to organ injury and failure. The injury occurring following hemorrhagic shock is unique in that there is a global insult to all organ systems. The inability to meet the cellular metabolic demands results in rapid tissue injury and organ dysfunction. Outward symptoms of HS include, e.g., reduced urine output (e.g., oliguria or anuria), delayed capillary refill, increased heart rate, cool and clammy skin, compromised mental status (e.g., confusion, agitation, or lethargy), weakness, and increased respiration rate.

Specification, paragraph [0037] (emphasis added). Similarly, *Webster's Medical Desk Dictionary* (1986) defines "shock" as:

> a state of profound depression of the vital processes of the body characterized by pallor, rapid but weak pulse, rapid and shallow respiration, restlessness, anxiety or mental dullness, nausea or vomiting associated with reduced total blood volume and low blood pressure and subnormal temperature resulting usu. from severe esp. crushing injuries, hemorrhage, burns, or major surgery...

(emphasis added; copy submitted herewith as Exhibit A). Although Fujita shows that CO improved survival of mice who had been subjected to experimentally induced lung ischemia, there is absolutely no indication in Fujita that the mice experienced hemorrhagic shock. The mice were not subjected to a reduction of circulating or total blood volume; rather, the left hilum of the lung, including the pulmonary artery, was clamped for a period of 1-1.5 hours to create an anemic condition in the lung tissue. There is no indication, or even suggestion, that the mice tested in Fujita experienced a significant reduction in circulating or total blood volume. Therefore, Fujita also does not inherently disclose treatment of hemorrhagic shock.

The Office cites Bar-Or as alleged evidence to support its argument that the art understood hemorrhagic shock to be a form of "generalized" ischemia. However, hemorrhagic shock involves more than ischemia alone. *Webster's Medical Desk Dictionary* (1986) defines "ischemia" as: "localized tissue anemia due to obstruction of the inflow of arterial blood" (emphasis added; copy submitted herewith as Exhibit B). Hemorrhagic shock, on the other hand,

is a systemic, multi-factorial condition that affects all organ systems (see Martel, 2002, "Hemorrhagic Shock," J. Obstet. Gynaecol. Can., 24:504-511; copy submitted herewith as Exhibit C). Martel states:

> In hemorrhagic shock, an acute reduction in blood volume leads to sympathetic compensation by peripheral vasoconstriction, tachycardia, and increased myocardial contractility, which in turn increases the myocardial demand for oxygen, to a level that cannot be maintained. Simultaneously, tissue hypoperfusion from precapillary vasoconstriction leads to anaerobic metabolism and acidosis. Tissue hypoxia, acidosis, and the release of various mediators lead to a systemic inflammatory response.

Martel page 3, right column. Martel also teaches that "the key systems affected by hemorrhagic shock are the central nervous, cardiac, and renal systems" (page 2, right column). However, these organs only experience hypoperfusion later in hemorrhagic shock, since "cardiac output is redirected to the most important organs: the heart, brain, and kidneys," early in the process (page 3, left column). Therefore, although ischemia of some organs may occur in hemorrhagic shock, ischemia is only one component of this condition. In fact, the most affected organs initially receive additional blood supply to compensate for the reduction in total blood volume. The redirection of blood flow to the brain, heart, and kidneys results in a concomitant reduction of blood flow to other organs. Therefore, although some ischemia does occur in the condition, hemorrhagic shock is more than simply "generalized ischemia." Because Fujita discloses only treatment of localized lung ischemia, and there is no evidence that the mice administered CO were subjected to hemorrhagic shock, Fujita provides no inherent teaching that of treatment of hemorrhagic shock with CO.

The Declaration of Brian S. Zuckerbraun, M.D., submitted herewith as Exhibit D, provides further support that hemorrhagic shock is recognized as being distinct from ischemia.

Fujita provides no express or inherent teaching or suggestion that CO can be used to treat hemorrhagic shock. Fujita only demonstrates that CO can provide protection against ischemia localized to the lung in animals not subjected to a loss of circulating or total blood volume. Therefore, the claims are novel over Fujita, and applicants request reconsideration and withdrawal of the rejection.

Claims 1-3 and 10-14 were rejected as allegedly inherently anticipated by Pinsky et al., US 2005/0048133 ("Pinsky"), as evidenced by Bar-Or. Applicants respectfully traverse.

As noted above, to anticipate a claim, a reference must teach, either expressly or inherently, every element of the claim. Pinsky provides no express or inherent teaching of hemorrhagic shock. Nowhere does Pinsky make any express disclosure related to hemorrhagic shock. Further, there is no inherent disclosure of hemorrhagic shock in Pinsky. The examples provided by Pinsky involve localized ischemia. In Example 7, Pinsky discloses that CO was protective in a cerebral ischemia model of stroke. In Example 11, Pinsky discloses that CO was protective against ischemic damage in a model of lung transplantation. There is no teaching or suggestion, nor has the Office provided any basis to conclude, that the animals suffered a significant reduction of circulating or total blood volume as observed in hemorrhagic shock. Thus, Pinsky does not anticipate the claimed methods.

Pinsky discloses that CO can be used to treated "ischemic disorders." Even if it is the Office's position that hemorrhagic shock is in some way a species of the genus of "ischemic disorders," Pinsky would still not inherently teach hemorrhagic shock. A reference that discloses a genus does not inherently disclose all species with that category. Rather, the reference must be examined to see if a disclosure of the claimed species has been made. See MPEP § 2112 IV, citing Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004). As noted above, Pinsky does not explicitly or inherently disclose treatment of hemorrhagic shock. Therefore, Pinsky does not inherently anticipate the claimed methods.

Pinsky provides no express or inherent teaching that CO can be used to treat hemorrhagic shock. Therefore, the claims are novel over Pinsky, and applicants request reconsideration and withdrawal of the rejection.

35 U.S.C. § 103

Claims 1, 55, and 56 were rejected as allegedly obvious over Fujita or Pinsky. The Office action alleges that Fujita or Pinsky anticipates claim 1, and one skilled in the art would be able to "discover optimum or workable ranges." However, applicants submit that neither Fujita nor Pinsky teaches or suggests the method of claim 1 (see above), because neither reference teaches or suggests the use of CO to treat the systemic condition of hemorrhagic shock. One skilled in the art would find no motivation in either reference or elsewhere in the art to administer CO for hemorrhagic shock. Similarly, one skilled in the art would find no motivation in Fujita, Pinsky, or elsewhere in the art to administer CO as recited in claim 55 or 56. Therefore, the claims are patentable over either Fujita or Pinsky, and applicants request reconsideration and withdrawal of the rejection.

Claims 1, 2, and 57-65 were rejected as allegedly obvious over Fujita or Pinsky in view of Peitzman et al., Curr. Probl. Surg., 1995, 32: 925-1002, abstract ("Peitzman"). Applicants submit that neither Fujita nor Pinsky anticipates the method of claim 1 or 2 (see above), because neither reference teaches explicitly or inherently the use of CO to treat the systemic condition of hemorrhagic shock. Peitzman is provided by the Office apparently for the limitation of blood transfusion. The Office has not alleged that Peitzman provides and Peitzman in fact provides no teaching or suggestion of the use of CO for treatment of hemorrhagic shock. Therefore, Peitzman fails to remedy the deficiencies of Fujita and Pinsky. Therefore, none of Fujita, Pinsky, or Peitzman, alone or in combination, would render the claims obvious. Therefore, the claims are patentable over either of Fujita or Pinsky in combination with Peitzman, and applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

This response is being submitted along with a Petition for Extension of Time and the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14022-0011001.

Respectfully submitted,

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